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(54) Title: USE OF ADENOSINE AGONISTS IN CANCER THERAPY

(57) Abstract

The present invention relates to pharmaceutical compositions for use in inducing proliferation of the hematopoietic system, in particular, of bone marrow cells, comprising a pharmaceutically acceptable carrier, excipient or diluent and, as an active ingredient, an effective amount of an adenosine A1 receptor agonist. The pharmaceutical composition of the present invention may be used to induce proliferation of bone marrow cells, in a variety of clinical situations where such proliferation is therapeutically beneficial. The active ingredient within the pharmaceutical composition of the invention may be a compound of general formula (I) or any other compound or substance which specifically binds to and/or activates the A1 adenosine receptor and acts as an agonist to the receptor's natural ligand.

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USE OF ADENOSINE AGONISTS IN CANCER THERAPY

FIELD OF THE INVENTION

This invention relates to drugs for use in cancer therapy. More specifically, the present invention concerns drugs which induce proliferation of cells of the hematopoietic system.

PRIOR ART

The following is a list of prior art references considered to be relevant as background to the invention:

1. Daly, J.W., Adenosine receptors: Targets for future drugs. *J. Med. Chem.*, **25**:197-207, 1982.
2. Stiles, G.L., Adenosine receptors and beyond: Molecular mechanisms of physiological regulation, *Clin. Res.*, **38**:10-18, 1990.
3. Collis, M.G., The vasodilator role of adenosine, *Pharmacol. Ther.*, **41**:143-162, 1989.
4. Fishman *et al.*, Extracellular adenosine acts as a chemoprotective agent, *Proceeding of the American Association for Cancer Research*, **39**:470, 1998.
5. Moos, W.H., et al.,N^6-cycloalkyladenosines. Potent A1-selective adenosine agonists, *J. Medicinal Chemistry* **28**:1383-1384, 1985.
6. Jacobson, K.A et al., Functionalized congeners of adenosine, *J. Medicinal Chemistry* **28**:1341-1346, 1985.
7. U.S. Patent No. 5,998,387.
8. U.S. Patent No. 5,998,388
9. U.S. Patent No. 5,498,605.
10. U.S. Patent No. 4,791,103.

BACKGROUND OF THE INVENTION

Adenosine is an extracellular messenger generated by all cells in the body. It is known to regulate different physiological processes within cells through binding to specific cell surface receptors – A1 and A2 receptors [1,2,3]. It was recently demonstrated that adenosine inhibits proliferation of tumor cells and induces proliferation of bone marrow cells[4]. Further more it was also shown that adenosine can protect white blood cells, particularly neutrophils, from destruction which is otherwise caused by chemotherapeutic drugs[4].

SUMMARY OF THE INVENTION

The present invention is based on the surprising findings that (i) the effect of adenosine in inducing proliferation of bone marrow cells can be inhibited by A1 receptor antagonists (antagonist that inhibits binding of adenosine to adenosine A1 receptor), and (ii) the effect of adenosine can be mimicked by an adenosine A1 receptor agonist (*"A1RAg"*). These findings led to the conclusion that the bone marrow proliferation-induction effect of adenosine is mediated, at least to some extent through the A1 receptor, and that accordingly A1RAg may be used to induce proliferation of bone marrow cells, in a wide variety of clinical situations where such proliferation is therapeutically beneficial.

The present invention provides, by a first of its aspects, a pharmaceutical composition for use in inducing proliferation of bone marrow cells, comprising a pharmaceutically acceptable carrier, excipient or diluent and, as an active ingredient, an effective amount of an A1RAg.

The present invention provides, by a second of its aspects, use of an A1RAg for the production of a pharmaceutical composition for use in inducing proliferation of bone marrow cells.

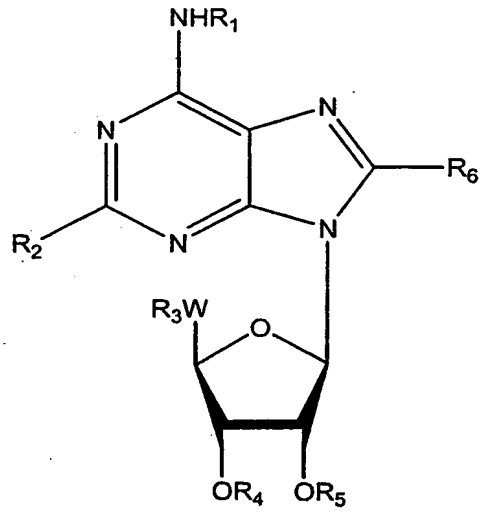
The present invention further provides a method of inducing proliferation of bone marrow cells in a subject, comprising administering to the subject an effective amount of an A1RAg.

The term *"effective amount"* used above and below should be understood as meaning an amount of an A1RAg which is capable of achieving a desired therapeutic effect, particularly, in inducing proliferation of bone marrow cells. The desired therapeutic effect depends on the type and mode of treatment. When, for example, said A1RAg is administered to counter drug-induced leukopenia, an effective amount thereof may be an amount which protects the treated subject against the drug-induced reduction in the count of leukocytes, particularly neutrophils; an amount of the active ingredient which can give rise to an increase in an already decreased level of such cells, e.g. restore the level to a normal level or sometimes even above; etc. The man of the art will have no difficulties, on the basis of a limited number of routine experiments, to determine an effective amount in each case.

As will be appreciated, the effective amount may also depend on the treated subject's gender, on the individual's weight, on the therapeutic regime, namely whether the A1RAg is administered once daily, several times daily, once in several days, etc. Furthermore, the effective amount may depend on the exact nature or etiology of the disease or condition which is being treated or intended to be prevented.

According to one embodiment of the invention, the A1RAg are adenosine derivatives carrying at least an N^6-substituent. Other positions may also be substituted. In fact, it has been found that the biological activity of an adenosine derivative may be enhanced by modifying other parts of the nucleotide, for example, at the 2- and/or 5'-positions (e.g. with chloro atoms). Such substituents were found to increase the molecule's A1 selectivity.

The adenosine derivatives which can be used according to the present invention are generally defined by the following formula (I):-

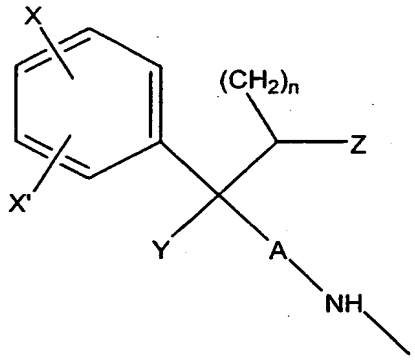


(I)

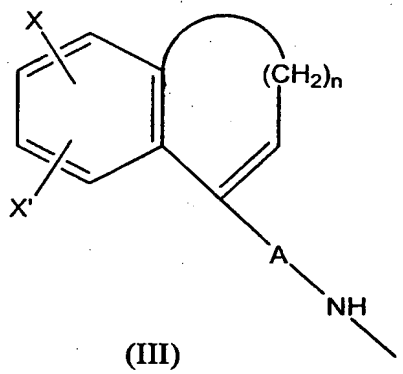
wherein

- R_1 represents a lower alkyl, cycloalkyl, preferably C_3-C_8 cycloalkyl (including the well known cyclohexyl and cyclopentyl containing derivatives, recognized as CPA and CHA, respectively), the cycloalkyl group may be substituted with, for example, a hydroxyl or lower alkyl; R_1 also represents a hydroxyl or hydroxyalkyl; a phenyl, anilide, or lower alkyl phenyl, all optionally substituted by one or more substituents, for example, halogen, lower alkyl, haloalkyl such as trifluoromethyl, nitro, cyano, $-(CH_2)_mCO_2R^a$, $-(CH_2)_mCONR_2R^aR^b$, $-(CH_2)_mCOR^a$, m representing an integer from 0 to 6; $-SOR^c$, $-SO_2R^c$, $-SO_3H$, $-SO_2NR^aR^b$, $-OR^a$, $-SR^a$, $-NHSO_2R^c$, $-NHCOR^a$, $-NR^aR^b$ or $-NHR^aCO_2R^b$; wherein
  - R^a and R^b represent independently a hydrogen, lower alkyl, alkanoyl, phenyl or naphthyl (the latter may be partially saturated) the alkyl group optionally being substituted with a substituted or unsubsituted phenyl or phenoxy group; or when R_1 represents $-NR^aR^b$, said R^a and R^b form

together with the nitrogen atom a 5- or 6- memebered heterocyclic ring optionally containing a second heteroatom selected from oxygen or nitrogen, which second nitrogen heteroatom may optionally be further substituted by hydrogen or lower alkyl; or $-NR^aR^b$ is a group of general formulae (II) or (III):-



(II)



(III)

wherein

- n is an integer from 1 to 4;
- Z is hydrogen, lower alkyl or hydroxyl;
- Y is hydrogen, lower alkyl, or OR' where R' is hydrogen, lower alkyl or lower alkanoyl;
- A is a bond or a lower alkylene, preferably, C_1-C_4 alkenyl; and
- X and X' are each independently hydrogen, lower alkyl, lower alkoxy, hydroxy, lower alkanoyl, nitro, haloalkyl such as trifluoromethyl, halogen, amino, mono- or di-lower alkyl amino, or when X and X' are taken together a methylenedioxy group;
- R^c represents a lower alkyl;

- R_2 represents a hydrogen; halogen; substituted or unsubsituted lower alkyl or alkenyl group; lower haloalkyl or haloalkenyl; cyano; acetoamido; lower alkoxy; lower alkylamino; NR^dR^e where R^d and R^e are independently hydrogen, lower alkyl, phenyl or phenyl substituted by lower alkyl, lower alkoxy, halogen or haloalkyl such as trifluoromethyl or alkoxyl; or $-SR^f$ where R^f is hydrogen, lower alkyl, lower alkanoyl, benzoyl or phenyl;

- W represents the group $-OCH_2-$, $-NHCH_2-$, $-SCH_2-$ or $-NH(C=O)-$;

- R_3, R_4 and R_5 represent independently a hydrogen, lower alkyl or lower alkenyl, branched or unbranched C_1-C_{12} alkanoyl, benzoyl or benzoyl substituted by lower alkyl, lower alkoxy, halogen, or R_4 and R_5 form together a five membered ring optionally substituted by a lower alkyl or alkenyl; R_3 further represents independently a phosphate, hydrogen or dihydrogen phosphate, or an alkali metal or ammonium or dialkali or diammonium said thereof;

- R_6 represents a hydrogen, halogen atom; or

- one of the R groups (i.e. R_1 to R_6) is a sulfohydrocarbon radical of the formula R^g-SO_3-R^h-, wherein R^g represents a group selected from C_1-C_{10} aliphatic, phenyl and lower alkyl substituted aromatic group which may be substituted or unsubstituted and R^h represents a monovalent cation. Suitable monovalent cations include lithium, sodium, potassium, ammonium or trialkyl ammonium, which will enable dissociation to take place under physiological conditions. The remaining R groups being a hydrogen or halogen atom, an unsubstituted hydrocarbon or any other non-sulfur containing group as defined above.

The active ingredient may be as defined above or in the form of salts or solvates thereof, in particular physiologically acceptable salts and solvates thereof. Further, when containing one or more asymmetric carbon atoms, the active ingredient may

include isomers and diastereoisomers of the compounds of formula (I) and mixtures thereof.

The hydrocarbon chains used herein may include straight or branched chains. In particular, the terms "alkyl" or "alkenyl" as used herein mean a straight or branched chain alkyl or alkenyl groups.

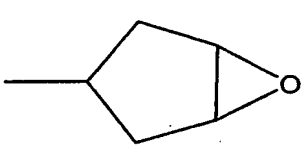
The terms "lower alkyl or lower alkenyl" mean respectively C_1-C_{10} alkyl or C_2-C_{10} alkenyl groups and preferably, C_1-C_6 alkyl and C_2-C_6 alkenyl groups.

Pharmaceutically acceptable salts of the compound of general formula (I) include those derived from pharmaceutically acceptable inorganic and organic acids. Examples of suitable acids include hydrochloric, hydrobromic, sulphoric, nitric, perchloric, fumaric, maleic, phosphoric, glycollic, lactic, salicylic, succinic, toluene-p-sulfonic, tartaric, acetic, citric, methanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic and benzenesulfonic acids.

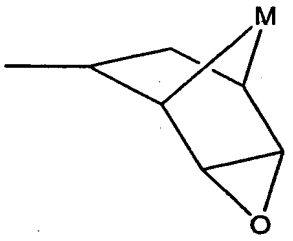
Preferred adenosine derivatives of formula (I) are the N^6-cyclopentyl adenosine (CPA), 2-chloro-CPA (CCPA), and N^6-cyclohexyl adenosine (CHA) derivatives, the preparation of which is well known to the person skilled in the art. Other adenosine derivatives which are known to be selective to the A1 receptor are those wherein R_1 is a anilide group, the latter may be unsubstituted or substituted for example with hydroxyl, alkyl, alkoxy or with a group $-CH_2C(O)R''$, R" being an hydroxyl group, $-NHCH_3$, $-NHCH_2CO_2C_2H_5$,(ethyl glycinate), tuloidide (also in which the methyl moiety is replaced with a haloalkyl moiety), or with a group $-CH_2C(O)NHC_6H_4CH_2C(O)R'''$, in which R''' represents a group to yield a methyl ester substituent ($-OCH_3$), an amide substituent (e.g. R''' being a group $-NHCH_3$), or R''' being a hydrazide, ethylenediamine, $-NHC_2H_5NHC(O)CH_3$, 4-(hydroxyphenyl)propionyl, biotinylated ethylene diamine or any other suitable hydrocarbon which renders the compound an A1 agonist. The preparation of some of the above specific adenosine derivatives is described in the art [5-8]

Alternatively, the N^6-substituted adenosine derivatives used as active ingredients according to the present invention may be those containing an epoxide moiety and more particularly are a cycloalkyl epoxy containing adenosine derivative (e.g. oxabicyclo such as norbornanyl or oxatricyclo such as adamantanyl). Some such compounds may be defined by general formula (I),

wherein R_1 is a group of general formulae (IVa) and (IVb):-



(IVa)



(IVb)

wherein M is a lower alkyl group as defined above.

Embodiments of the agonist compounds having an epoxide N^6-norbornyl group include the endo and exo isomers and more particularly, can be one of four isomers: the 2R-exo, 2R-endo, 2S-exo and 2S-endo form.

Another embodiment of the N^6-norbornyl derivative may include an oxygen atom at the N^1-position of the purine ring. This compound is termed N^6-(5,6-epoxynorborn-2-yl)adenosine-1-oxide.

At times, the active ingredient may be an adenine derivative in which the β-D-ribofuranozyl moiety of adenosine is replaced with a hydrogen or phenyl group.

The invention has a wide range of therapeutic utilities and provides treatment for a wide range of diseases, disorders or conditions in both human and non-human animals, where induction of proliferation of bone marrow cells may be beneficial to the

treated subject. Therapeutic applications include immunomodulation in a subject having a weak immune system, for example: as a result of a genetic disorder; as a result of an infection by an infectious agent, e.g. a virus; as a result of a general stress situation, e.g. following a car or another accident, etc.; as a result of a treatment which causes reduction in the level of leukocytes, particularly neutrophils, e.g. a chemotherapy or treatment with a neuroleptic drug; etc.

A treatment according to the invention may be used to reduce the risk of infection resulting from congenital or acquired neutropenias.

The present invention may also be used for the treatment of subjects having a low count of white blood cells, either a general low count or a count of a specific class of white blood cells, e.g. neutrophils. A weakened immune system manifested by a reduction in white blood cell count, is often seen in cancer patients, and when this occurs, this may have a severe effect on the treated patent, and may at times even be a cause of death. In such a case it is thus important to try and increase the white blood cell count. This may be achieved by the treatment in accordance with the invention.

Reduction of white blood cell count, particularly of neutrophils, is very often an undesired side effect of a variety of treatments, including: anti-cancer therapy by chemotherapy or radiotherapy; treatment of a subject with neuroleptic drugs; etc. The active ingredient of the invention may be used in such subject to counter these undesired side effects of the treatment. In accordance with some therapeutic regimes, the active ingredient of the invention may be administered prior to such treatment, or concurrently therewith. For example, in the case of a treatment with a chemotherapeutic drug or treatment with a neuroleptic drug, the active ingredient of the invention may be administered either prior to the onset of treatment with the chemotherapeutic or the neuroleptic drug during such treatment, or may also at times be given after such treatment. In other words, the active ingredient of the invention may be used either as a preventive agent, namely to prevent reduction of the white blood cell level as a result of the treatment, or may be used as an acute therapeutic agent for simulating an increase in

the level of the white blood cells after the level was reduced as a result of said treatment.

In accordance with one embodiment of the invention, an anti-cancer chemotherapeutic agent or a neuroleptic drug may be combined in one formulation with the active ingredient of the invention.

BRIEF DESCRIPTION OF THE FIGURES

In order to understand the invention and to see how it may be carried out in practice, a preferred embodiment will now be described, by way of non-limiting example only, with reference to the accompanying drawings, in which:

Fig. 1 is a bar graph showing results of an *in vitro* assay in which proliferation of bone marrow cells was tested without adenosine (dense stripes) and with adenosine (spaced stripes) together with adenosine A1 receptor antagonist (DPCPX) and adenosine A2 receptor antagonist (DMPX) as compared to a control without any additional added drug. The bar graph shows results of a [^{3}H]thymidine incorporation assay.

Fig. 2 shows [^{3}H]thymidine incorporation assay of a control bone marrow cell preparation (*"control"*), in the presence of adenosine (*"control+ adenosine"*) and in the presence of two different concentrations of an A1 receptor agonist, (*"CPA"*).

DETAILED DESCRIPTION OF A PREFERRED EMBODIMENT

The invention will now be illustrated by the following description of some experiments carried out according thereto.

MATERIALS AND METHODS

Mice

Female ICR or C57BL/6J mice aged 3 months, weighing an average of 25g were used. The mice were purchased from Harlan Laboratories, Jerusalem, Israel. Standardized pelleted diet and tap water were supplied.

Drugs

All drugs were purchased from Sigma Chemical Co. St. Louis, MO. Adenosine was dissolved in water and kept as a stock solution in a concentration of 1mM. For *in vitro* studies, dilutions in RPMI medium were carried out and final concentrations of 100, 50, 25, 10 and 5μM were used. For *in vivo* studies, the stock solution was diluted with PBS to a concentration of 3mM and 0.5 ml was injected intraperitoneally to mice. 1,3-dipropyl-8-cyclopentylxanthine (DPCPX), an adenosine A1 receptor antagonist, 3,7-dimethyl-1-propargyl-xantane (DMPX) an A2 receptor antagonist and N-cyclopentyladenosine (CPA), a selective A1 receptor agonist were added to a culture of proliferating bone marrow cells.

Evaluation of bone marrow cell proliferation *in vitro*

Bone marrow cells were obtained from the femur of C57BL/6J mice. Cells were disaggregated by passing through a 25G needle. [^{3}H]-Thymidine incorporation assay was used to evaluate the proliferative capability of the bone marrow cells.

Cells ($3x10^4$ /well) were incubated with RPMI medium, containing 10% fetal calf serum (FCS) (Biological Industries, Beit Haemek, Israel) and adenosine, adenosine antagonists or the agonist in 96 microtiter plates for 48h. Cultures containing cells were suspended in RPMI medium and 10% FCS served as controls. In the last 6 hours of incubation, each well was pulsed with 1μCi [^{3}H]-thymidine. Cells were harvested and the ^{3}[H] -thymidine uptake was determined in an LKB liquid scintillation counter (LKB, Piscataway, NJ, USA).

RESULTS

Effect of adenosine, adenosine receptor antagonists and agonist on bone marrow cell proliferation

Exposure of bone marrow cells to adenosine at concentrations of 10-50μM stimulated ^{3}[H] –thymidine incorporation in a concentration dependent manner (Fishman *et al.*[4]).

To evaluate which adenosine receptor is responsible for this stimulatory effect, two adenosine receptor antagonists were used, i.e., DPCPX (A1 antagonist) and DMPX (A2 antagonist). The effect of the antagonists on bone marrow cell proliferation was examined with and without adenosine. In the absence of adenosine, the effect of endogenous adenosine which is released by the bone marrow cells and affects the same cells by a paracrine way, was evaluated. DPCPX (0.1 μM) which block the A1 receptor, significantly reversed the stimulatory effect of adenosine on bone marrow cell proliferation. DMPX (0.1 μM) given without or with adenosine induced a stimulatory effect on bone marrow cell proliferation (Fig 1). These results show that the A1 receptor is responsible for the stimulatory effect of adenosine. To confirm this result, CPA, a selective adenosine A1 receptor agonist was added to a culture of bone marrow cells. CPA induced a statistically significant stimulation of bone marrow cell proliferation at concentrations of 0.1 and 0.01 μM (Fig 2).

CLAIMS

1. A pharmaceutical composition for use in inducing proliferation of bone marrow cells, comprising a pharmaceutically acceptable carrier, excipient or diluent and, as an active ingredient, an effective amount of an adenosine A1 receptor agonist.

2. A pharmaceutical composition according to Claim 1, for use as an immunomodulator.

3. A pharmaceutical composition according to Claim 1 or 2, for use in treatment of a subject having a low white blood cell count.

4. A pharmaceutical composition according to Claim 1 or 2, for use in treating cancer patients.

5. A pharmaceutical composition according to Claim 4, for use in increasing level of white blood cells in a cancer patient whose white blood count was reduced as a result of chemotherapy or radiotherapy.

6. A pharmaceutical composition according to Claim 1 or 2, for treating a subject undergoing a drug treatment which may cause reduction in leukocytes level.

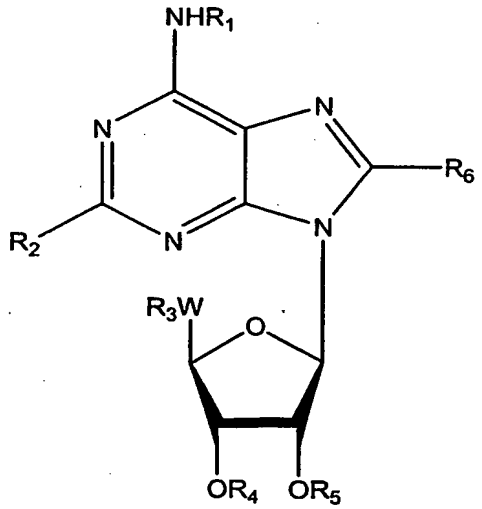
7. A pharmaceutical composition according to Claim 1 or 2, for administering to a subject undergoing a treatment which may cause reduction in neutrophils level in order to prevent said reduction.

8. A pharmaceutical composition according to Claim 6 or 7, wherein said treatment is a treatment with an anti-cancer chemotherapeutic drug or a neuroleptic drug.

9. A pharmaceutical composition comprising an effective amount of an anti-cancer chemotherapeutic agent in combination with an effective amount of an adenosine A1 receptor agonist and a pharmaceutical acceptable carrier, excipient or diluent.

10. A pharmaceutical composition comprising an effective amount of a neuroleptic drug in combination with an effective amount of an adenosine A1 receptor agonist and a pharmaceutical acceptable carrier, excipient or diluent.

11. A pharmaceutical composition according to Claim 1, 9 or 10, wherein said adenosine A1 receptor agonist is a compound of general formula (I):-

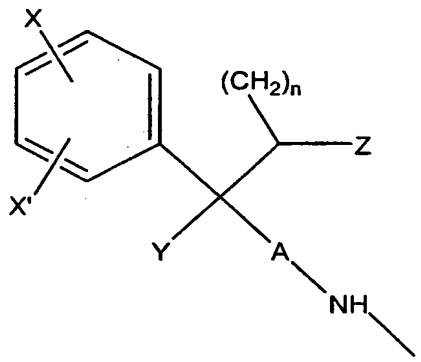


(I)

wherein

- R_1 represents a lower alkyl, substituted or unsubstituted cycloalkyl; a hydroxyl or hydroxyalkyl; a phenyl, anilide, or lower alkyl phenyl, all optionally substituted by one or more substituents; $-SOR^c$, $-SO_2R^c$, $-SO_3H$, $-SO_2NR^aR^b$, $-OR^a$, $-SR^a$, $-NHSO_2R^c$, $-NHCOR^a$, $-NR^aR^b$, or $-NHR^aCO_2R^b$; wherein
  - R^a and R^b represent independently a hydrogen, lower alkyl, alkanoyl, amine, phenyl or naphthyl, the alkyl group optionally being substituted with a substituted or unsubsituted phenyl or phenoxy group; or when R_1 represents $-NR^aR^b$, said R^a and R^b form together with the nitrogen atom a 5- or 6- memebered heterocyclic ring optionally containing a second heteroatom selected from oxygen or nitrogen, which second nitrogen

heteroatom may optionally be further substituted by hydrogen or lower alkyl; or $-NR^aR^b$ is a group of general formulae (II) or (III):-



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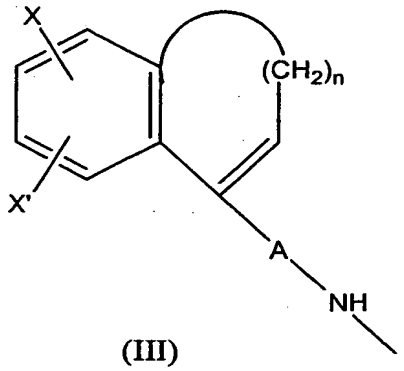


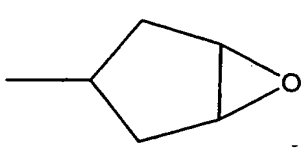
(III)

wherein n an integer from 1 to 4; Z is hydrogen, lower alkyl or hydroxyl; Y is hydrogen, lower alkyl, or OR' where R' is hydrogen, lower alkyl or lower alkanoyl; A is a bond or a lower alkylene, preferably, C_1-C_4 alkenyl; X and X' are each independently hydrogen, lower alkyl, lower alkoxy, hydroxy, lower alkanoyl, nitro, haloalkyl such as trifluoromethyl, halogen, amino, mono- or di-lower alkyl amino, or when X and X' are taken together a methylenedioxy group;

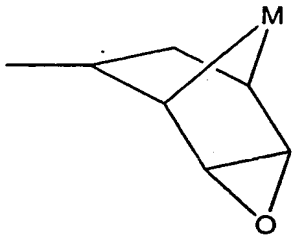
- R^c represents a lower alkyl;

or

- R_1 represents an epoxide substitutent of general formulae (IVa) or (IVb):



(IVa)



(IVb)

wherein M is a lower alkyl group;

- R_2 represents hydrogen; halogen; substituted or unsubsituted lower alkyl or alkenyl group; lower haloalkyl or alkenyl; cyano; acetoamido; lower alkoxy; lower alkylamino; NR^dR^e where R^d and R^e are independently hydrogen, lower alkyl, phenyl or phenyl substituted by lower alkyl, lower alkoxy, halogen or haloalkyl or alkoxyl; $-SR^f$ where R^f is hydrogen, lower alkyl, lower alkanoyl, benzoyl or phenyl;

- W represents the group $-OCH_2-$, $-NHCH_2-$, $-SCH_2-$ or $-NH(C=O)-$;

- R_3, R_4 and R_5 represent independently a hydrogen, lower alkyl or lower alkenyl, branched or unbranched C_1-C_{12} alkanoyl, benzoyl or benzoyl substituted by lower alkyl, lower alkoxy, halogen, or R_4 and R_5 form together a 5-membered ring optionally substituted by a lower alkyl or alkenyl; R_3 further represents independently a phosphate, hydrogen or dihydrogen phosphate, or an alkali metal or ammonium or dialkali or diammonium said thereof;

- R_6 represents a hydrogen or halogen atom; or

- one of the substituents R_1 to R_6 is a sulfohydrocarbon radical of the formula R^g-SO_3-R^h-, wherein R^g represents a group selected from C_1-C_{10} aliphatic, phenyl and lower alkyl substituted aromatic group which may be substituted or

unsubstituted and R^h represents a monovalent cation, and the non-sulfur containing substituents being as defined above;

and isomers, diastereomers, pharmaceutically acceptable salts or solvates of said compound.

12. Use of an adenosine A1 receptor agonist for the production of a pharmaceutical composition for use in inducing proliferation of bone marrow cells.

13. Use according to Claim 12, for the production of an immunomodulator pharmaceutical composition.

14. Use according to Claim 12 or 13, for the production of a pharmaceutical composition for the treatment of subjects having a low white blood cell count.

15. Use according to Claim 14, wherein the pharmaceutical composition is intended for use in treating cancer patients.

16. Use according to Claim 15, wherein the pharmaceutical composition is intended for use in increasing level of white blood cells in a cancer patient whose white blood count was reduced as a result of chemotherapy or radiotherapy.

17. Use according to Claim 12 or 13, wherein the pharmaceutical composition is intended for use in treating a subject undergoing a drug treatment, which may cause reduction in leukocytes level.

18. Use according to Claim 12 or 13, wherein the pharmaceutical composition is intended for administration to subjects undergoing a treatment, which may cause reduction in neutrophils level, in order to prevent said reduction.

19. Use according to Claim 17 or 18, wherein said treatment is a treatment with an anti-cancer chemotherapeutic drug or a neuroleptic drug.

20. Use of a combination of an anti-cancer chemotherapeutic drug and an adenosine A1 receptor for the production of a pharmaceutical composition.

21. Use of a combination of a neuroleptic drug and an adenosine A1 receptor for the production of a pharmaceutical composition.

22. A method of inducing proliferation of bone marrow cells in a subject, comprising administering to the subject an effective amount of an adenosine A1 receptor agonist.

23. A method according to Claim 22, comprising administering the adenosine A1 receptor agonist to a subject having a low white blood cell count.

24. A method according to Claim 22 or 23, wherein the treated subject is a cancer patient.

25. A method according to Claim 24, wherein the treated subject is a cancer patient whose white blood cells level was reduced as a result of chemotherapy or radiotherapy.

26. A method for preventing reduction in level of leukocytes in a subject as a result of a treatment comprising administering to the individual an effective amount of an adenosine A1 receptor agonist.

27. A method according to Claim 26, wherein said treatment is a drug treatment.

28. A method according to Claim 27, wherein the drug is an anti-cancer chemotherapeutic drug or a neuroleptic drug.

29. A method of treatment of an individual comprising administering to the subject a therapeutic drug in combination with an adenosine A1 receptor agonist.

30. A method according to Claim 29, wherein the therapeutic drug is an anti-cancer chemotherapeutic drug or a neuroleptic drug.

31. A method according to Claim 29 or 30, wherein the adenosine A1 receptor agonist is administered prior or during a course of administration of the therapeutic drug.

AMENDED CLAIMS

[received by the International Bureau on 16 May 2000 (16.05.00);
original claims 1-31 replaced by new claims 1-28 (12 pages)]

1. Use of an adenosine A1 receptor agonist for the production of a pharmaceutical composition for inducing proliferation of bone marrow cells.

2. Use according to Claim 1, for the production of an immunomodulator pharmaceutical composition.

3. Use according to Claim 1 or 2, for the production of a pharmaceutical composition for the treatment of subjects having a low white blood cell count.

4. Use according to Claim 3, wherein the pharmaceutical composition is intended for use in treating cancer patients.

5. Use according to Claim 4, wherein the pharmaceutical composition is intended for use in increasing the level of white blood cells in a cancer patient whose white blood count was reduced as a result of chemotherapy or radiotherapy.

6. Use according to Claim 4 or 5, wherein the pharmaceutical composition is intended for use in treating a subject undergoing a drug treatment, which may cause reduction in leukocytes level.

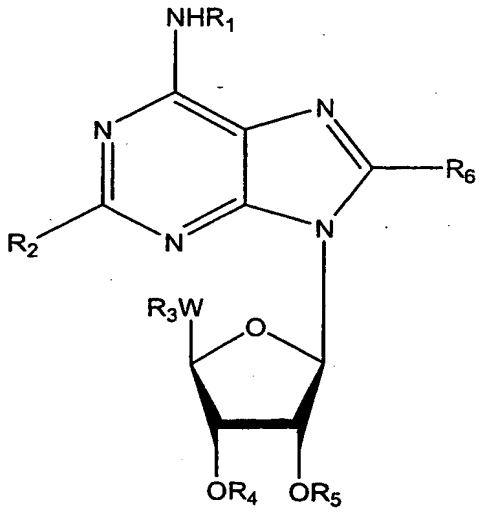
7. Use according to Claim 1 or 2, wherein the pharmaceutical composition is intended for administration to subjects undergoing a treatment, which may cause reduction in neutrophil level, in order to prevent said reduction.

8. Use according to Claim 6 or 7, wherein said treatment is a treatment with an anti-cancer chemotherapeutic drug or a neuroleptic drug.

9. Use of a combination of an anti-cancer chemotherapeutic drug and an adenosine A1 receptor agonist for the production of a pharmaceutical composition.

10. Use of a combination of a neuroleptic drug and an adenosine A1 receptor agonist for the production of a pharmaceutical composition.

11. Use according to any one of Claims 1 to 10, wherein said A1 adenosine receptor agonist is a compound of the general formula (I):

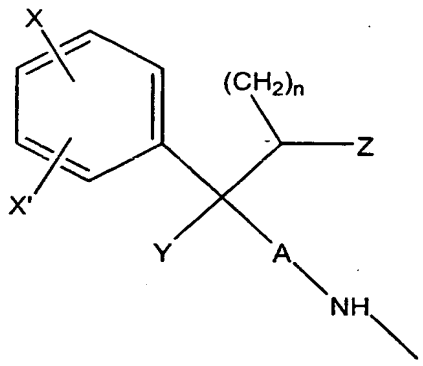


(I)

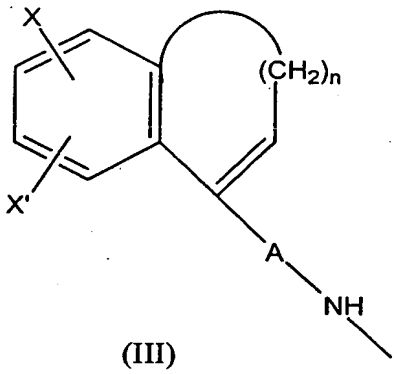
wherein

- R_1 represents a lower alkyl, substituted or unsubstituted cycloalkyl; a hydroxyl or hydroxyalkyl; a phenyl, anilide, or lower alkyl phenyl, all optionally substituted by one or more substituents; $-SOR^c$, $-SO_2R^c$, $-SO_3H$, $-SO_2NR^aR^b$, $-OR^a$, $-SR^a$, $-NHSO_2R^c$, $-NHCOR^a$, $-NR^aR^b$, or $-NHR^aCO_2R^b$; wherein

  - R^a and R^b represent independently a hydrogen, lower alkyl, alkanoyl, amine, phenyl or naphthyl, the alkyl group optionally being substituted with a substituted or unsubsituted phenyl or phenoxy group; or when R_1 represents $-NR^aR^b$, said R^a and R^b form together with the nitrogen atom a 5- or 6- memebered heterocyclic ring optionally containing a second heteroatom selected from oxygen or nitrogen, which second nitrogen heteroatom may optionally be further substituted by hydrogen or lower alkyl; or $-NR^aR^b$ is a group of general formulae (II) or (III):-



(II)



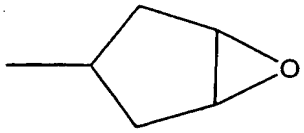
(III)

wherein n is an integer from 1 to 4; Z is hydrogen, lower alkyl or hydroxyl; Y is hydrogen, lower alkyl, or OR' where R' is hydrogen, lower alkyl or lower alkanoyl; A is a bond or a lower alkylene, preferably, C_1-C_4 alkenyl; X and X' are each independently hydrogen, lower alkyl, lower alkoxy, hydroxy, lower alkanoyl, nitro, haloalkyl such as trifluoromethyl, halogen, amino, mono- or di-lower alkyl amino, or when X and X' are taken together a methylenedioxy group;

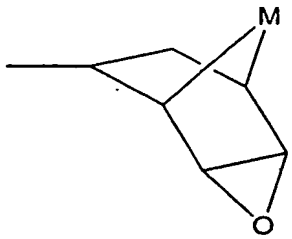
- R^c represents a lower alkyl;

or

- R_1 represents an epoxide substitutent of general formulae (IVa) or (IVb):



(IVa)



(IVb)

wherein M is a lower alkyl group;

- R_2 represents hydrogen; halogen; substituted or unsubsituted lower alkyl or alkenyl group; lower haloalkyl or alkenyl; cyano; acetoamido; lower alkoxy; lower alkylamino; NR^dR^e where R^d and R^e are independently hydrogen, lower alkyl, phenyl or phenyl substituted by lower alkyl, lower alkoxy, halogen or haloalkyl or alkoxyl; $-SR^f$ where R^f is hydrogen, lower alkyl, lower alkanoyl, benzoyl or phenyl;

- W represents the group $-OCH_2-$, $-NHCH_2-$, $-SCH_2-$ or $-NH(C=O)-$;

- R_3, R_4 and R_5 represent independently a hydrogen, lower alkyl or lower alkenyl, branched or unbranched C_1-C_{12} alkanoyl, benzoyl or benzoyl substituted by lower alkyl, lower alkoxy, halogen, or R_4 and R_5 form together a 5-membered ring optionally substituted by a lower alkyl or alkenyl; R_3 further represents independently a phosphate, hydrogen or dihydrogen phosphate, or an alkali metal or ammonium or dialkali or diammonium said thereof;

- R_6 represents a hydrogen or halogen atom; or

- one of the substituents R_1 to R_6 is a sulfohydrocarbon radical of the formula R^g-SO_3-R^h-, wherein R^g represents a group selected from C_1-C_{10} aliphatic, phenyl and lower alkyl substituted aromatic group which may be substituted or

unsubstituted and R^h represents a monovalent cation, and the non-sulfur containing substituents being as defined above;

and isomers, diastereomers, pharmaceutically acceptable salts or solvates of said compound.

12. Use according to Claim 11, wherein said adenosine A1 receptor agonist is selected from the group consisting of N^6-cyclopentyl adenosine (CPA), 2-chloro-CPA (CCPA), and N^6-cyclohexyl adenosine (CHA).

13. A method of inducing proliferation of bone marrow cells in a subject, comprising administering to the subject an effective amount of an adenosine A1 receptor agonist.

14. A method according to Claim 13, comprising administering the adenosine A1 receptor agonist to a subject having a low white blood cell count.

15. A method according to Claim 13 or 14, wherein the treated subject is a cancer patient.

16. A method according to Claim 15, wherein the treated subject is a cancer patient whose white blood cells level was reduced as a result of chemotherapy or radiotherapy.

17. A method for preventing reduction in level of leukocytes in a subject as a result of a treatment comprising administering to the individual an effective amount of an adenosine A1 receptor agonist.

18. A method according to Claim 17, wherein said leukocytes are neutrophils.

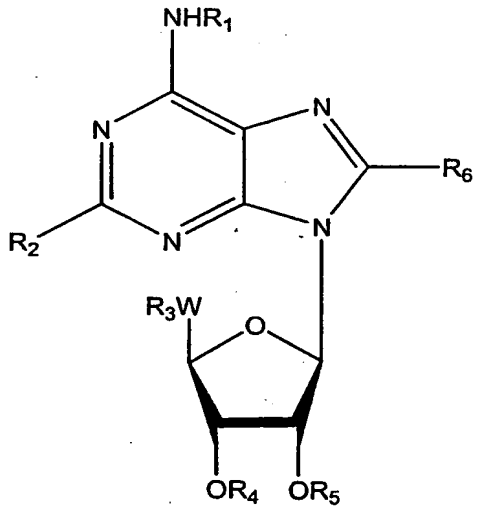
19. A method according to Claim 17 or 18, wherein said treatment is a drug treatment.

20. A method according to Claim 19, wherein said drug is an anti-cancer chemotherapeutic drug or a neuroleptic drug.

21. A method of treatment of an individual comprising administering to the subject a therapeutic drug in combination with an adenosine A1 receptor agonist.

22. A method according to Claim 29 or 30, wherein the adenosine A1 receptor agonist is administered prior or during a course of administration of the therapeutic drug.

23. A method according to any one of Claims 13 to 22, wherein said adenosine A1 receptor agonist is a compound of general formula (I):-



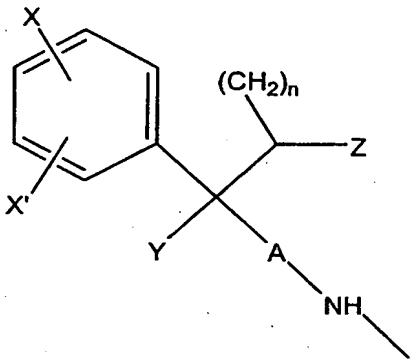
(I)

wherein

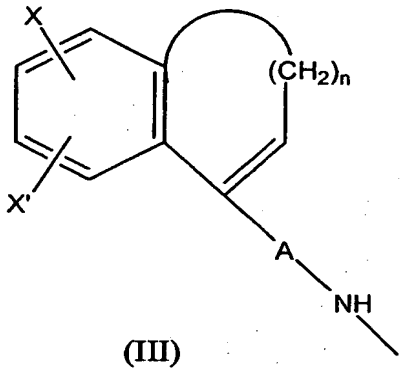
- R_1 represents a lower alkyl, substituted or unsubstituted cycloalkyl; a hydroxyl or hydroxyalkyl; a phenyl, anilide, or lower alkyl phenyl, all optionally substituted by one or more substituents; $-SOR^c$, $-SO_2R^c$, $-SO_3H$, $-SO_2NR^aR^b$, $-OR^a$, $-SR^a$, $-NHSO_2R^c$, $-NHCOR^a$, $-NR^aR^b$, or $-NHR^aCO_2R^b$; wherein

  - R^a and R^b represent independently a hydrogen, lower alkyl, alkanoyl, amine, phenyl or naphthyl, the alkyl group optionally being substituted with a substituted or unsubsituted phenyl or phenoxy group; or when R_1 represents $-NR^aR^b$, said R^a and R^b form together with the nitrogen atom a 5- or 6- memebered heterocyclic ring optionally containing a second

heteroatom selected from oxygen or nitrogen, which second nitrogen heteroatom may optionally be further substituted by hydrogen or lower alkyl; or $-NR^aR^b$ is a group of general formulae (II) or (III):-



(II)



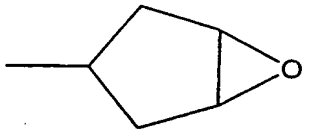
(III)

wherein n is an integer from 1 to 4; Z is hydrogen, lower alkyl or hydroxyl; Y is hydrogen, lower alkyl, or OR' where R' is hydrogen, lower alkyl or lower alkanoyl; A is a bond or a lower alkylene, preferably, C_1-C_4 alkenyl; X and X' are each independently hydrogen, lower alkyl, lower alkoxy, hydroxy, lower alkanoyl, nitro, haloalkyl such as trifluoromethyl, halogen, amino, mono- or di-lower alkyl amino, or when X and X' are taken together a methylenedioxy group;

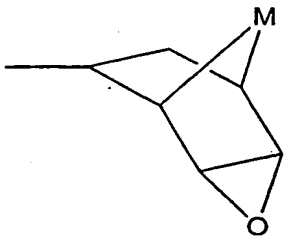
- R^c represents a lower alkyl;

or

- R_1 represents an epoxide substituent of general formulae (IVa) or (IVb):



(IVa)



(IVb)

wherein M is a lower alkyl group;

- R_2 represents hydrogen; halogen; substituted or unsubsituted lower alkyl or alkenyl group; lower haloalkyl or alkenyl; cyano; acetoamido; lower alkoxy; lower alkylamino; NR^dR^e where R^d and R^e are independently hydrogen, lower alkyl, phenyl or phenyl substituted by lower alkyl, lower alkoxy, halogen or haloalkyl or alkoxyl; $-SR^f$ where R^f is hydrogen, lower alkyl, lower alkanoyl, benzoyl or phenyl;

- W represents the group $-OCH_2-$, $-NHCH_2-$, $-SCH_2-$ or $-NH(C=O)-$;

- R_3, R_4 and R_5 represent independently a hydrogen, lower alkyl or lower alkenyl, branched or unbranched C_1-C_{12} alkanoyl, benzoyl or benzoyl substituted by lower alkyl, lower alkoxy, halogen, or R_4 and R_5 form together a 5-membered ring optionally substituted by a lower alkyl or alkenyl; R_3 further represents independently a phosphate, hydrogen or dihydrogen phosphate, or an alkali metal or ammonium or dialkali or diammonium said thereof;

- R_6 represents a hydrogen or halogen atom; or

- one of the substituents R_1 to R_6 is a sulfohydrocarbon radical of the formula R^g-SO_3-R^h-, wherein R^g represents a group selected from C_1-C_{10} aliphatic, phenyl and lower alkyl substituted aromatic group which may be substituted or

unsubstituted and R^h represents a monovalent cation, and the non-sulfur containing substituents being as defined above;

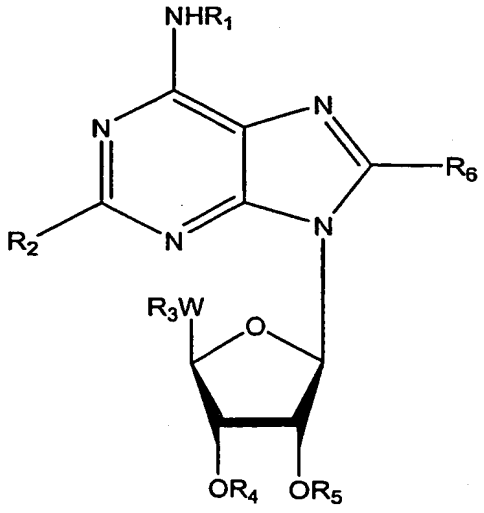
and isomers, diastereomers, pharmaceutically acceptable salts or solvates of said compound.

24. The method according to Claim 23, wherein said compound is selected from the group consisting of N^6-cyclopentyl adenosine (CPA), 2-chloro-CPA (CCPA), and N^6-cyclohexyl adenosine (CHA).

25. A pharmaceutical composition comprising an effective amount of an anti-cancer chemotherapeutic agent in combination with an effective amount of an adenosine A1 receptor agonist and a pharmaceutical acceptable carrier, excipient or diluent.

26. A pharmaceutical composition comprising an effective amount of a neuroleptic drug in combination with an effective amount of an adenosine A1 receptor agonist and a pharmaceutical acceptable carrier, excipient or diluent.

27. A pharmaceutical composition according to Claim 25 or 26, wherein said adenosine A1 receptor agonist is a compound of general formula (I):-

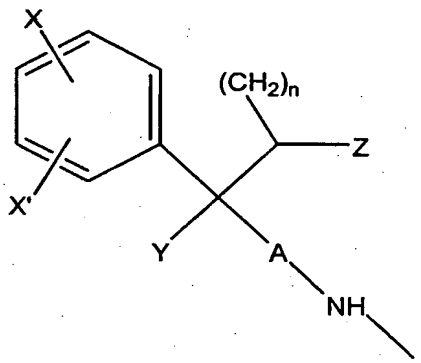


(I)

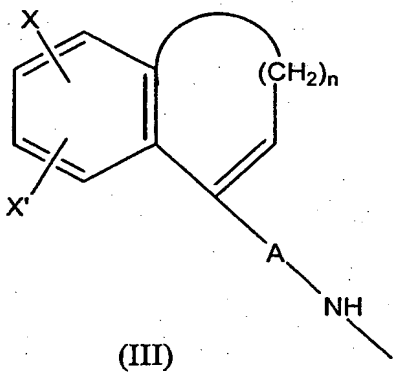
wherein

- R_1 represents a lower alkyl, substituted or unsubstituted cycloalkyl; a hydroxyl or hydroxyalkyl; a phenyl, anilide, or lower alkyl phenyl, all optionally substituted by one or more substituents; $-SOR^c$, $-SO_2R^c$, $-SO_3H$, $-SO_2NR^aR^b$, $-OR^a$, $-SR^a$, $-NHSO_2R^c$, $-NHCOR^a$, $-NR^aR^b$, or $-NHR^aCO_2R^b$; wherein

- R^a and R^b represent independently a hydrogen, lower alkyl, alkanoyl, amine, phenyl or naphthyl, the alkyl group optionally being substituted with a substituted or unsubsituted phenyl or phenoxy group; or when R_1 represents $-NR^aR^b$, said R^a and R^b form together with the nitrogen atom a 5- or 6- memebered heterocyclic ring optionally containing a second heteroatom selected from oxygen or nitrogen, which second nitrogen heteroatom may optionally be further substituted by hydrogen or lower alkyl; or $-NR^aR^b$ is a group of general formulae (II) or (III):-



(II)



(III)

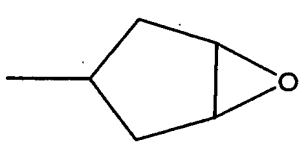
wherein n an integer from 1 to 4; Z is hydrogen, lower alkyl or hydroxyl; Y is hydrogen, lower alkyl, or OR' where R' is hydrogen, lower alkyl or lower alkanoyl; A is a bond or a lower alkylene, preferably, C_1-C_4 alkenyl; X and X' are each independently hydrogen, lower alkyl, lower alkoxy, hydroxy, lower alkanoyl, nitro, haloalkyl such as trifluoromethyl, halogen, amino, mono- or

di-lower alkyl amino, or when X and X' are taken together a methylenedioxy group;

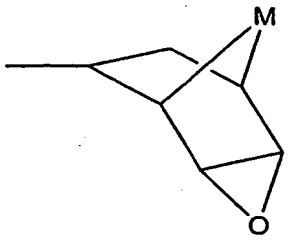
- R^c represents a lower alkyl;

or

- R_1 represents an epoxide substituent of general formulae (IVa) or (IVb):



(IVa)



(IVb)

wherein M is a lower alkyl group;

- R_2 represents hydrogen; halogen; substituted or unsubsituted lower alkyl or alkenyl group; lower haloalkyl or alkenyl; cyano; acetoamido; lower alkoxy; lower alkylamino; NR^dR^e where R^d and R^e are independently hydrogen, lower alkyl, phenyl or phenyl substituted by lower alkyl, lower alkoxy, halogen or haloalkyl or alkoxyl; $-SR^f$ where R^f is hydrogen, lower alkyl, lower alkanoyl, benzoyl or phenyl;

- W represents the group $-OCH_2-$, $-NHCH_2-$, $-SCH_2-$ or $-NH(C=O)-$;

- R_3, R_4 and R_5 represent independently a hydrogen, lower alkyl or lower alkenyl, branched or unbranched C_1-C_{12} alkanoyl, benzoyl or benzoyl substituted by lower alkyl, lower alkoxy, halogen, or R_4 and R_5 form together a 5-membered ring optionally substituted by a lower alkyl or alkenyl; R_3 further represents independently a phosphate, hydrogen or dihydrogen phosphate, or an alkali metal or ammonium or dialkali or diammonium said thereof;

- R_6 represents a hydrogen or halogen atom; or

- one of the substituents R_1 to R_6 is a sulfohydrocarbon radical of the formula R^g-SO_3-R^h-, wherein R^g represents a group selected from C_1-C_{10} aliphatic, phenyl and lower alkyl substituted aromatic group which may be substituted or unsubstituted and R^h represents a monovalent cation, and the non-sulfur containing substituents being as defined above;

and isomers, diastereomers, pharmaceutically acceptable salts or solvates of said compound.

28. The pharmaceutical composition according to Claim 27, wherein said adenosine A1 receptor agonist is selected from the group consisting of N^6-cyclopentyl adenosine (CPA), 2-chloro-CPA (CCPA), and N^6-cyclohexyl adenosine (CHA).

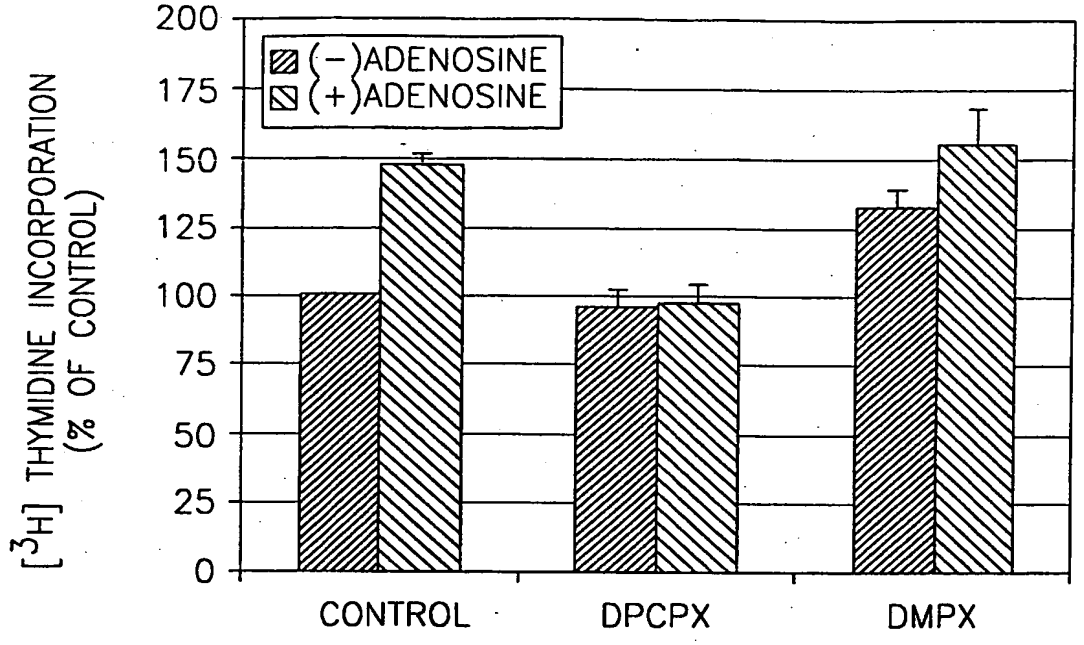

200
175
150
125
100
75
50
25
0
(−)ADENOSINE
(+)ADENOSINE
[3H] THYMIDINE INCORPORATION (% OF CONTROL)
CONTROL
DPCPX
DMPX

FIG.1

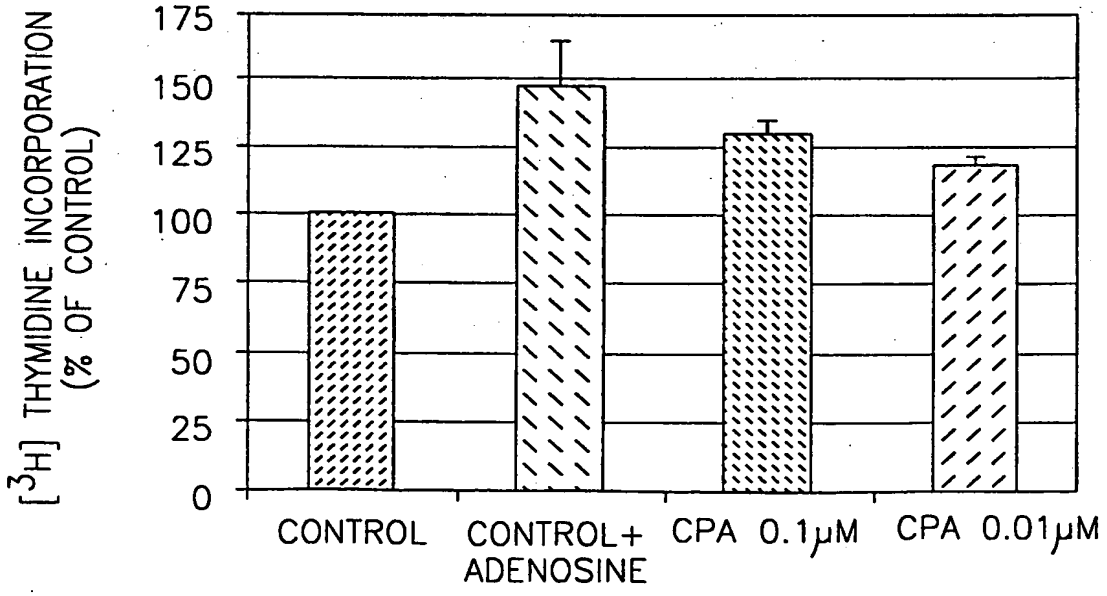

175
150
125
100
75
50
25
0
[3H] THYMIDINE INCORPORATION (% OF CONTROL)
CONTROL
CONTROL+ ADENOSINE
CPA 0.1μM
CPA 0.01μM

FIG.2

INTERNATIONAL SEARCH REPORT

Intern nal Application No
PCT/IL 00/00014

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/70 C07H19/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 24363 A (UNIVERSITY OF FLORIDA) 10 July 1997 (1997-07-10) claims 1-5,26--30 page 3, line 21 - line 29 & US 5 998 387 A cited in the application	1-8,11
X	WO 97 43300 A (GLAXO GROUP LTD) 20 November 1997 (1997-11-20) claims 1-17 & US 5 998 388 A cited in the application	1-8,11
X	WO 94 02497 A (THE UNITED STATES OF AMERICA) 3 February 1994 (1994-02-03) claims 1-23 & US 5 498 605 A cited in the application	1-8,11

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 April 2000	20/04/2000

Name and mailing address of the ISA	Authorized officer
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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter. nal Application No
PCT/IL 00/00014

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 791 103 A (B. K. TRIVEDI ET AL) 13 December 1998 (1998-12-13) cited in the application claims 1-48	1-8,11
X	WILLIAMS M: "PURINERGIC DRUGS: OPPORTUNITIES IN THE 1990S" DRUG DEVELOPMENT RESEARCH,US,NEW YORK, NY, vol. 28, no. 3, 1 March 1993 (1993-03-01), pages 438-444, XP002046590 ISSN: 0272-4391 page 439, left-hand column -right-hand column	1-8
A	MOOS W H ET AL: "N6-CYCLOALKYLADENOSINES. POTENT A1-SELECTIVE ADENOSINE AGONISTS" JOURNAL OF MEDICINAL CHEMISTRY,US,AMERICAN CHEMICAL SOCIETY. WASHINGTON, vol. 28, no. 10, 1 October 1985 (1985-10-01), pages 1383-1384, XP002038896 ISSN: 0022-2623 cited in the application	1-31
A	H B TEY ET AL: "ADENOSINE MODULATES CELL GROWTH IN HUMAN EPIDERMOID CARCINOMA (A431) CELLS" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS,US,ACADEMIC PRESS INC. ORLANDO, FL, vol. 187, no. 3, 30 September 1992 (1992-09-30), pages 1486-1492-1492, XP002102065 ISSN: 0006-291X	1-19

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL 00/00014

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 22-31
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 22-31 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-10 and 12-21 relate to a composition containing an active agent defined by reference to a desirable characteristic or property, namely having agonist activity for the adenosine A1 receptor, as well as the use of these compositions for inducing proliferation of the cells of the hematopoietic system.
The claims cover all compositions containing compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compositions. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compositions by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compositions containing the compounds of formula (I) as disclosed in claim 11 of the present application, either alone or in combination with other agents, and their use in inducing proliferation of the hematopoietic system.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter ...nal Application No
PCT/IL 00/00014

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